Ph.D. Thesis Synopsis

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Biological evaluation of Nanoformulated Anti-cancer agent: A Multifaceted approach to improve bioavailability, multi drug resistance and apoptotic cell death

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Title: Biological evaluation of Nanoformulated Anti-cancer agent: A Multifaceted approach to improve bioavailability, multi drug resistance and apoptotic cell death

Abstract:

Cancer is a global epidemic and the second leading cause of death worldwide. In the current scenario, incidences and mortality rates of cancer are increasing gradually. The recent advances in cancer therapy such as surgery, chemotherapy, radiotherapy and immunotherapy, exhibit adverse side effects such as systemic toxicities, immune surveillance and drug resistance. In clinical practices chemotherapy is the most often offered therapy against cancer, but cancer cells acquire chemoresistance over a short span of treatment with anti-cancer drugs. Therefore, development of Multidrug resistance (MDR) is the major obstacle in successful cancer therapeutic regimens. In recent past, several attempts have been made to overcome the MDR in cancer, but it is still challenging. Therefore, there is a constant demand to address this life-threatening disease with new alternative therapies. Natural derivatives from medicinal plants have been used to treat a number of human diseases including cancer in many parts of the world since ancient times. Over 60% of clinically used anti-cancer agents were derived from natural recourses. Growing research is drawing its attention to explore natural plant derived active molecules for anti-cancer therapy. The natural bioactive molecules could be promising anti-cancer agents due to limited side effects and multi-targeting responses as they can block more than one signaling pathway. However, poor bioavailability including limited solubility, systemic toxicity, renal clearance, metabolic degradation and impermeability in crossing the blood-brain and intestinal barriers limits the application of natural flavonoids for cancer therapy. Therefore, the need of an hour is to revolutionize the drug delivery system by improving the bioavailability and therapeutic index of natural plant derivatives. In the present study, we have used natural plant derivative curcumin and translated in nano sized using pluronic block co-polymer (Pluronic®F127) with an aim to improve its solubility in aqueous medium. Further, we have examined its biological response including anti-proliferative, apoptotic and anti-inflammatory responses in MCF-7 and MCF-7/R (drug resistant) cells. The results revealed that Pluronic micelles encapsulated curcumin improve solubility, cellular uptake, inhibit cell proliferation and release of pro-inflammatory cytokines in MCF-7 and MCF7/R cells as compared to the free curcumin. This approach may offer a new strategy to improve the drug delivery system for cancer therapy.

1. Introduction:

Cancer is a complex disease, which is an outcome of a depreciated array of precisely controlled cell processes like cell division and cell death. It is the second leading cause of death and socio-economic problem worldwide [1]. The normal cell acquires a number of alterations and becomes malignant. These alterations include; Self- sufficiency to grow, Evasion of apoptosis, Insensitivity towards growth Inhibitors, Immortalization, Angiogenesis, Invasion of tissue and metastasis, Deregulated metabolism, Evading the immune system, Unstable DNA, Inflammation and development of drug resistance [2]. Chemotherapy is the most recommended therapy and plays a vital role in treating numbers of cancer but it is challenging due to systemic toxicity, reoccurrence and development of multi-drug resistant (MDR) phenomenon [3, 4]. Majority of chemotherapeutic drugs approved by the FDA are of lower molecular weight and require a higher concentration for their pharmacological actions. Many anti-cancer drugs act indiscriminately adjacent to cancerous and healthy cells. The acquisition of resistance to chemotherapy is a major hurdle in cancer therapeutics [5, 6]. Although many types of cancers show susceptibility towards chemotherapy at the initial stage, after some time, they acquire resistance due to multiple intrinsic and extrinsic factors such as cellular reprogramming, oncogenic stimulation, drug efflux due to over expression of multidrug resistant genes, metabolic changes that promote drug inactivation, drug target alteration, DNA damage repair mechanism, inhibition of programmed cell death, epithelial mesenchymal transition (EMT), inherent cell heterogeneity, epigenetic changes, or any combination of these mechanisms [7].

Multidrug resistance (MDR) is a phenomenon in which the malignant cells become insensitive to anticancer drugs and attain the ability to survive even after several exposures of anticancer agents [8]. The immune surveillance also may impair due to the unpredictable cell death escape strategies acquired by cancer cells [6]. Several biochemical changes have been identified in multidrug resistant cells, the most consistent of which is the increased expression of P-glycoprotein. P-glycoprotein, a conserved high molecular weight plasma membrane glycoprotein is the first discovered human ABC transporter (encoded by the ABCB1 [adenosine Triphosphate binding cassette, subfamily B, member 1] gene). It holds the central position in multidrug resistant cells by diminishing the intracellular accumulation of chemotherapeutic agents [9]. P-gp can export an astonishing variety of amphipathic drugs, natural products, and peptides from mammalian cells, in ATP dependant manner. The ATP binding domain of P-gp provides the energy required for a conformational change that transfers the drug against very steep concentration gradients [10].

Recent advances in nanotechnology have shown a greater interest in drug delivery system [11]. In past decades several molecules have been identified with excellent biological

properties but could not be used as a drug due to poor bioavailability including limited solubility, renal clearance, metabolic degradation, systemic toxicity and impermeability in crossing the blood-brain and intestinal barriers [12]. Therefore, application of nano carriers could be the best approach to accomplish specific delivery of a drug at the desire site, for desire time and at desire concentration. Various biodegradable nano carriers are being used for improving drug delivery [13]. Pluronic block copolymers have been emerging as a nanocarrier in a drug delivery system for minimizing drug degradation, improving stability upon administration, excluding undesirable side effects provoked by chemotherapeutic agents and improving bioavailability of hydrophobic drugs [14]. Pluronics are amphiphilic in nature and block copolymers of hydrophilic poly-(ethylene oxide) (PEO) and hydrophobic poly-(propylene oxide) (PPO). They are arranged in A-B-A tri-block structure: PEO-PPO-PEO and also known as “poloxamers”[15].

Pluronics are known to have surfactant properties and an ability to interact with hydrophobic surfaces and biological membranes. Above critical micelle concentration (CMC), these copolymers self-assemble into micelles in aqueous solution [16]. The core of micelles comprises hydrophobic poly-(propylene oxide) (PPO), which represents “cargo hold” for incorporation of hydrophobic molecules. The hydrophobic nature of PPO core makes micelles suitable to protect the molecules or drugs from chemical degradation and rapid metabolism. Hydrophilic poly-(ethylene oxide) (PEO) shells decrease undesirable drug interactions and ensure that micelles remain in a dispersed state [17]. Pluronics can sensitize multidrug resistant tumors towards anticancer agents and enhance the transportation of drugs across the blood-brain barrier and intestinal barrier [15]. Thus, application of pluronics has impending therapeutic significance in the drug delivery system.

Curcumin (1,7-Bis (4-hydroxy-3-methoxyphenyl) -1,6-heptadiene- 3,5-Dione) is a natural polyphenolic compound derived from the rhizome of the plant Curcuma longa [18, 19]. Since decades, it has been used as a traditional medicine. Despite the wide spectrum of biological activities of curcumin, its pharmacological applications are limited due to low solubility in the aqueous medium (11 ng/mL in aqueous buffer), rapid degradation at physiological pH,[20] lower absorption in the gastrointestinal tract,[21] and rapid systemic elimination [22].

In the present study, we have synthesized aqueous soluble pluronic micelles encapsulated curcumin and characterized by various biophysical methods. Next, we examined its anti-proliferative, anti-inflammatory response and explored the molecular mechanism for the induction of apoptotic cell death in human breast adenocarcinoma (MCF-7) cells and drug resistant human breast adenocarcinoma (MCF-7/R) cells.

2. Hypothesis:

Cancer is the second leading cause of death worldwide. Treatment options for cancer such as surgery, chemotherapy, radiotherapy, and immunotherapy have undesirable side effects such as systemic toxicities, recurrence, and drug resistance. Acquisition of multidrug resistance in cancer is the major obstacle in the successful application of cancer therapeutics. However, natural flavonoids are seemed to be better alternatives of chemotherapeutic agents. Curcumin is a natural derivative that exhibits broad spectrum biological activities including anti-oxidant, anti-inflammatory, and anti-cancer. Despite its imperative properties, the pharmacological applications have been limited due to low solubility in the aqueous medium, limited tissue absorption, and rapid degradation at physiological pH. The present study aimed to apply the nanotechnological approach for encapsulation of curcumin in Pluronic block co-polymer which may improve its stability, solubility, anti-cancer, and anti-inflammatory efficacy. Moreover, this curcumin loaded nanocarrier may sensitize drug resistant cancer cells. Therefore, the defined objective of the present study is to synthesize the Pluronic micelles encapsulated curcumin which may conquer the poor solubility, improve sustainability and efficacy of curcumin. The study will also elucidate the ability of this nanoformulation to combat drug resistance in cancer.

These were the major objectives to achieve the aim of the study.

3. Objectives:

1. Synthesize and characterization of anti-cancer molecules in nanocarrier.
2. In vitro evaluation of toxicity and inhibition in cell viability by Nanoformulatated anti-cancer agent in different origin of cancer cells.
3. Study the effect of Nanoformulatated anti-cancer agent in cellular uptake and mode of cell death signaling.
4. To establish and characterize Multiple Drug Resistant (MDR) cell lines and to check the permeability of Nanoformulation.
5. To evaluate the effect of Nanoformulations on inhibition of cell proliferation and induction of cell death in MDR cancer cells.
6. To check the effects of Nanoformulation on expression and regulation of respective MDR genes involved in drug resistance and detection of cross-resistance to anti-cancer drug.
7. To check the effects of Nanoformulation on inflammatory mediators in MDR cells.

4. Methodology:

1. **Synthesize and characterization of anti-cancer molecules in nanocarrier**.
   Pluronic micelles encapsulated curcumin (PMsCur) was synthesized by thin-film hydration method and characterized by Dynamic light scattering (DLS), Small angle neutron scattering analysis (SANS), UV-Visible spectroscopy (UV-VIS), Fourier transform infrared spectroscopy (FT-IR), Powder X-ray diffraction spectroscopy (PXRD), and Differential scanning calorimetry (DSC).

2. **In vitro evaluation of toxicity and inhibition in cell viability by Nanoformulatated anti-cancer agent in different origin of cancer cells.**
   Inhibition in cell proliferation and cell viability were tested by MTT and Trypan Blue assay in MCF-7, HCT-116, HEK 293T and NIH-3T3 cells.

3. **Study the effect of Nanoformulatated anti-cancer agent in cellular uptake and mode of cell death signaling.**
   The release of curcumin from PMsCur was analyzed by In vitro drug release study. Uptake of curcumin in MCF-7 was by examined by cellular uptake assay. The underlying mechanism of cell death was analyzed by Annexin-V/ Propidium Iodide staining, Flow cytometry and western blotting. The mitochondrial membrane potential was analyzed by JC-1 probe and Mitotracker Red Dye. Intracellular ROS generation was monitored by H_2DCFDA dye and ROS mediated cell death was evaluated by MTT assay in presence and absence of inhibitor NAC (ROS scavenger). Cytotoxicity study of PMsCur was conducted by LDH assay kit. The effect of PMsCur on clonogenic ability and migration ability of MCF-7 cells was analyzed by Colony formation assay and Wound healing assay.

4. **To establish and characterize Multiple Drug Resistant (MDR) cell lines and to check the permeability of Nanoformulation.**
   Drug resistant human breast adenocarcinoma cells (MCF-7/R) were developed by transfection of plasmid expression vectors encoding human MDR-1 gene for P-glycoprotein (P-gp) in MCF-7 cells. Further, MCF-7/R cells were characterized by western blot analysis, Real Time-PCR analysis, Rhodamine 123 accumulation assay and Doxorubicin uptake assay.

5. **To evaluate the effect of Nanoformulation on inhibition of cell proliferation and induction of cell death in MDR cancer cells.**
   Effect of PMsCur on inhibition in cell proliferation and cell viability of MCF-7/R were determined by MTT, CFDA and Trypan Blue assay. The uptake of curcumin in MCF-

7/R was examined by cellular uptake assay. Effect of PMsCur on cell death signaling was analyzed by Annexin –V/PI staining, Flow cytometry analysis and western blot analysis in MCF-7/R cells. The mitochondrial membrane potential was analyzed by JC-1 probe in MCF-7/R cells. Cytotoxicity study of PMsCur was conducted by LDH assay kit. The intracellular level of ATP was examined by ATP assay kit. Effect of PMsCur on accumulation of Rhodamine was analyzed by Rhodamine 123 uptake assay.

6. **To check the effects of Nanoformulation on expression and regulation of respective MDR genes involved in drug resistance and detection of cross-resistance to anti-cancer drug.**

   Effect of PMsCur on expression of MDR associated genes in MCF-7/R cells was analyzed by Western blotting and Real-Time PCR analysis. Further, effect of PMsCur on Epithelial to Mesenchymal Transition (EMT) was also analyzed by Western blotting and Real-Time PCR analysis in MCF-7/R cells. Drug sensitivity assay was performed to examine the effect of known anti-cancer drug Doxorubicin and Colchicine on MCF-7 and MCF-7/R cells.

7. **To check the effects of Nanoformulation on inflammatory mediators in MDR cells.**

   Activity of NF-κB was monitored by assessing the translocation of GFP tagged p65 (GFP-p65), luciferase reporter assay and western blotting in MCF-7 and MCF-7/R cells. The levels of pro-inflammatory cytokines were monitored by ELISA assay, Western blot analysis, and Real-Time PCR analysis in MCF-7 and MCF-7/R cells.

5. The following salient findings were achieved from the present study:

1. **Synthesis and biophysical characterization revealed successful formulation of Pluronic micelles encapsulated curcumin (PMsCur):** Pluronic micelles encapsulated curcumin (PMsCur) synthesized by thin film hydration method, and characterized by Dynamic light scattering (DLS), Small angle neutron scattering analysis (SANS), UV-Visible spectroscopy (UV-VIS), Fourier transform infrared spectroscopy (FT-IR), Powder X-ray diffraction spectroscopy (PXRD), and Differential scanning calorimetry (DSC) which confirmed that Curcumin was incorporated in Pluronic F127. Pluronic micelles encapsulated curcumin (PMsCur) significantly improved the aqueous solubility and stability of curcumin as compared to free curcumin.

2. **PMsCur exhibits sustained release and enhanced cellular uptake of curcumin**

   In vitro drug release study showed that PMsCur exhibits the slow and sustained release of curcumin at physiological pH. Next, we examined the cellular uptake of curcumin by utilizing its intrinsic autofluorescence property. We observed intense fluorescence of curcumin in PMsCur treated cells as compared to the free curcumin. These results suggest that PMsCur augments cellular uptake with the slow and sustained release of curcumin in MCF-7 cells.

3. **PMsCur inhibits cell proliferation, cell viability, clonogenic and migration ability of cancer cells**

   Pluronic micelles encapsulated curcumin (PMsCur) significantly inhibits cell proliferation in different origin of cancer and transformed cells (MCF-7, HCT 116, HEK 293T), but does not show inhibition of cell proliferation on NIH 3T3 cells (normal mouse fibroblast cells). Further, the cell death was analyzed by Trypan blue exclusion assay. The results showed that the different origin of cancer cells treated with PMsCur exhibit higher percent of cell death as compared to those treated with the free curcumin. PMsCur significantly inhibits the clonogenic and migration ability of MCF-7 cells as compared to the free curcumin. Thus, results revealed PMsCur significantly inhibits cell proliferation and induce cell death as compared to free curcumin in different origin of cancer cells.

4. **PMsCur induces apoptosis by activation of caspase cascades, decreasing the mitochondrial membrane potential and arrest cell cycle in G0/G1 phase in MCF-7/R cells**

   Pluronic micelles encapsulated curcumin (PMsCur) induces programmed cell death by decreasing mitochondrial membrane potential and with subsequent activation of caspases cascade for induction of apoptosis in MCF-7 cells. Moreover, PMsCur exhibits ROS-dependent cell death and restricts necrotic cell death in MCF-7 cells. Importantly, PMsCur arrests cell cycle in G0/G1 phase in MCF-7 cells

5. **Drug resistant human breast adenocarcinoma cells (MCF-7/R) was established and characterization shows development of drug resistance phenomenon in MCF-7/R cells**

   The expression of P-glycoprotein (P-gp/MDR1) is associated with the drug resistance in cancer cells. P-glycoprotein is known to play a significant role in drug resistance by

acting as an energy-dependent efflux pump to eliminate or inactivate chemotherapeutic agents from the cell before they can exert their cytotoxic effects. Drug resistant human breast adenocarcinoma cells (MCF-7/R) were established by overexpression of P- glycoprotein in MCF-7 cells. Characterization of MCF-7/R cells shows significant increase in the expression of P-gp as compared to MCF-7. The elevated expression of CD44v6 (a cancer stem cell marker) and Nrf-2, associated with the development of drug resistance, were also observed in MCF-7/R cells. Further, we found that MCF-7/R cells reduce the accumulation of Rhodamine 123 and uptake of Doxorubicin due to P-gp mediated efflux in MCF-7/R cells. Collectively our results suggest the development of drug resistant phenomenon in MCF-7/R cells.

6. **MCF-7/R shows resistance against Doxorubicin and Colchicine while PMsCur inhibits proliferation and clonogenic ability of MCF-7/R cells and augment cellular uptake of curcumin.**

   MCF-7/R cells show a high level of resistance against chemotherapeutic agent Doxorubicin and Colchicine as compared to MCF-7 cells. Interestingly, Pluronic micelles encapsulated curcumin (PMsCur) sensitize MCF-7/R cells by inhibition in cell proliferation and induction of cell death. Moreover, PMsCur did not show the cytotoxic effect on normal human mammary epithelial cells (MCF-10A). We have also examined the cellular uptake of curcumin by utilizing its intrinsic autofluorescence property. We observed intense fluorescence of curcumin in PMsCur treated cells as compared to the free curcumin. PMsCur augments cellular uptake of curcumin and significantly inhibits the clonogenic ability of MCF-7/R cells as compared with the free curcumin.

7. **PMsCur induces apoptosis by decreasing the mitochondrial membrane potential, improves the cellular uptake of Rhodamine 123 and deplete the intracellular ATP level in MCF-7/R cells**

   PMsCur decreases the mitochondrial membrane potential and induces apoptosis by activation of caspase cascade in MCF-7/R cells. PMsCur significantly increase the cellular uptake of Rhodamine 123 in MCF-7/R cells. Moreover, the mechanisms of dug efflux transporters gain the energy by ATP. PMsCur decreases the intracellular level of ATP in MCF-7/R cells. Interestingly, PMsCur does not exhibit necrotic cell death in MCF-7/R and MCF-10A.

8. **PMsCur negatively regulates the expression of MDR associated genes and Epithelial to Mesenchymal Transition (EMT) in MCF-7/R cells**

PMsCur significantly downregulates the expression of genes associated with drug resistance such as P-glycoprotein, CD44v6 and Nrf-2. PMsCur also negatively regulates and inhibits Epithelial to Mesenchymal Transition (EMT) the in MCF-7/R cells.

9. PMsCur attenuates inflammatory response in MCF-7 and MCF-7/R cells

The nuclear transcription factor NF-κB is a pivotal mediator of inflammatory response and involved in the regulation of cell proliferation and survival. We found that PMsCur efficiently inhibits the activation of NF-kB as compared to the free curcumin in MCF-7 and MCF-7/R cells. Moreover, PMsCur also inhibit the release of pro-inflammatory cytokines in MCF-7 and MCF-7/R cells as compared to the free curcumin. Collectively, PMsCur attenuates the inflammatory response by inhibiting activity of NF-kB and release of pro-inflammatory cytokines in MCF-7 and MCF-7/R cells.

6. Conclusion:

- Pluronic micelles encapsulated curcumin (PMsCur) improves the solubility and cellular uptake of Curcumin.
- Pluronic micelles encapsulated curcumin (PMsCur) enhance anti-cancer efficacy of Curcumin and manifests apoptosis in cancer cells.
- PMsCur sensitize drug resistant cancer cells and promotes apoptotic cell death.
- PMsCur significantly improves the anti-inflammatory efficacy of curcumin in drug sensitive as well as drug resistant cancer cells.
- PMsCur is non-toxic to the normal cells.
- It was noteworthy that anti-proliferative response of PMsCur was more promising in MCF7/R cells.

Take together, these findings suggest that PMsCur is the promising candidate for harnessing multidrug resistance and inhibition of cell proliferation in cancer. It could be a stable formulation for improving drug delivery in cancer. This approach could offer a new stratagem for efficient drug delivery of anti-cancer agents and may provide a possible revolution in regimens of cancer therapeutics.

7. References:

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13. Pathak, C., F.U. Vaidya, and S.M. Pandey, *Mechanism for development of nanobased drug delivery System*, in *Applications of Targeted Nano Drugs and Delivery Systems*. 2019, Elsevier. p. 35-67.
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- **LIST OF PUBLICATIONS:**

1. **Foram U. Vaidya**, Abu S. Chhipa, Vinita Mishra, Vishal Kumar Gupta, Shiv Govind Rawat, Ajay Kumar and Chandramani Pathak **(2020)** Molecular and Cellular Paradigms of Multidrug Resistance in Cancer. **Cancer Reports** (Under Major Revision)
2. Reena R. Varma, Juhee G. Pandya, **Foram U. Vaidya**, Chandramani Pathak, Bhupesh S. Bhatt and Mohan N. Patel **(2020)** Biological activities of pyrazoline-indole based Re(I) carbonyls: DNA interaction, antibacterial, anticancer, ROS production, lipid peroxidation, in vivo and in vitro cytotoxicity studies. **Chemico-Biological Interactions** (Under Revision)
3. Nikita J. Patel, Bhupesh S. Bhatt, Pankaj A. Vekariya, **Foram U. Vaidya**, Chandramani Pathak, Juhi G. Pandya, Bhupesh S. Bhatt and Mohan N. Patel **(2020)** Synthesis, characterization, structural-activity relationship and biomolecular interaction studies of heteroleptic Pd(II) complexes with acetyl pyridine scaffold. **Journal of Molecular Structure** DOI: https://doi.org/10.1016/j.molstruc.2020.128802
4. Bharat H. Pursuwani, Bhupesh S. Bhatt, **Foram U. Vaidya**, Chandramani Pathak and Mohan N. Patel **(2020)** Oxadiazole based Os(IV) compounds as potential DNA intercalator and cytotoxic agents. **Inorganic Chemistry Communications** 108070. https://doi.org/10.1016/j.inoche.2020.108070
5. Darshana N. Kanthecha, Bhupesh S. Bhatt, Dilip B. Raval, Vasudev R. Thakkar, **Foram U. Vaidya**, Chandramani Pathak, Mohan N. Patel **(2020)** Bipyrazole based novel bimetallic μ-oxo bridged Au(III) complexes as potent DNA interacalative, genotoxic, anticancer, antibacterial and cytotoxic agents. **Journal of Inorganic and Organometallic Polymers and Materials**. DOI: https://doi.org/10.1007/s10904-020-01618-2
6. Bhupesh S. Bhatt, Divyang H. Gandhi, **Foram U. Vaidya**, Chandramani Pathak & Tushar N. Patel **(2020)** Cell apoptosis induced by ciprofloxacin based Cu(II) complexes: Cytotoxicity, SOD mimic and antibacterial studies, **Journal of Biomolecular Structure and Dynamics**, DOI: 10.1080/07391102.2020.1776641
7. Bharat H. Pursuwani, Bhupesh S. Bhatt, **Foram U. Vaidya**, Chandramani Pathak & Mohan N. Patel **(2020)** Tetrazolo[1,5-a]quinoline moiety-based Os(IV) complexes: DNA binding/cleavage, bacteriostatic and photocytotoxicity assay, **Journal of Biomolecular Structure and Dynamics**, DOI: 10.1080/07391102.2020.1756912
8. **Foram U. Vaidya**, Rakesh Sharma, Sofiya Shaikh, Debes Ray, Vinod K. Aswal and Chandramani Pathak **(2019)** Pluronic micelles encapsulated Curcumin manifests apoptotic cell death and inhibits pro-inflammatory cytokines in Human breast adenocarcinoma cells. **Cancer Reports**,2:1-e1133. https://doi.org/10.1002/cnr2.1133

9. Shanaya Patel, Bhargav Waghela, Kanisha Shah, **Foram Vaidya**, Sheefa Mirza, Saumya Patel, Chandramani Pathak & Rakesh Rawal **(2018)** Silibinin, A Natural Blend In Polytherapy Formulation For Targeting Cd44v6 Expressing Colon Cancer Stem Cells. **Nature Scientific Reports**, 8(1):16985 DOI:10.1038/s41598-018-3506900
10. Miral V. Lunagariya, Khyati P. Thakor, Bhargav N. Waghela, **Foram U. Vaidya**, Chadramani Pathak & Mohan N. Patel **(2018)** Design, synthesis, MTT assay, DNA interaction studies of platinum(II) complexes. **Journal of Biomolecular Structure & Dynamics** 36(1):14-31, DOI: 10.1080/07391102.2016.1268071.

- **BOOK CHAPTERS:**

1. Chandramani Pathak, **Foram U. Vaidya**, Bhargav N. Waghela, Abu Sufiyan Chhipa, Budhi Sagar Tiwari and Kishu Ranjan **(2020)** Advanced glycation end products mediated oxidative stress and regulated cell death signalling in cancer. (Submitted, Springer Nature)
2. **Foram U. Vaidya**, Abu Sofiyan Chhipa, Nibha Sagar and Chandramani Pathak **(2020)** Oxidative stress and inflammation can fuel cancer; In Maurya et al. (Eds) Role of oxidative stress in pathophysiology of disease. Springer, Singapore. DOI: https://doi.org/10.1007/978-981-15-1568-2_14. ISBN: 978-981-15-1567-5
3. Chandramani Pathak, **Foram U. Vaidya** and Shashibahl M. Pandey **(2019)** Mechanism for Development of Nanobased Drug Delivery System. In Mohapatra et al. (Eds) Applications of Targeted Nano Drugs and Delivery Systems Nanoscience and Nanotechnology in Drug Delivery: A volume in Micro and Nano Technologies. DOI https://doi.org/10.1016/C2017-0-00274-4; ISBN 978-0-12-814029-1; Imprint Elsevier

- **PATENT:**

1. Chandramani Pathak, Vinita Mishra, Shikha Tiwari, Bhargav N. Waghela, **Foram U. Vaidya**, Neha Kapoor, Dinesh Kumar; "Novel Caffeic Acid Analogsas Toll-like receptor 4 Antagonists" Indian patent filed, 27th Sept 2019. Application No. 201921039249

- **PRESENTATIONS IN CONFERENCES/ SYMPOSIA**

1. INTERNATIONAL CONFERENCE : **Foram U. Vaidya**, Chandramani Pathak presented poster on “Pluronic Micelles Encapsulated Curcumin Potentiates Apoptosis And Anti- inflammatory Response In Drug Resistant Human Breast Adenocarcinoma Cells” in ASCB EMBO MEETING, held on 7th-11th December, 2019 at Washington Convention centre, Washington, USA
2. **Foram U. Vaidya**, Kishu Ranjan, Bhargav N. Waghela and Chandramani Pathak presented Rapid fire poster on “Non-canonical role of FADD in regulation of NLRP-3 mediated Inflammasome and cell death” in 3rd Annual Conference of Society of Inflammation Research , held on 13th October, 2019 at Sankara Nethralaya, Chennai
3. **Foram U. Vaidya** and Chandramani Pathak presented Oral Talk on “Effect of Pluronic Micelles encapsulated Curcumin on drug resistant human breast adenocarcinoma cells” in National Symposium on Basic & Translational Research in Cancer Biology, held on 11th-12th September, 2019 at Institute of Advanced Research, Gandhinagar Gujarat, India (Best Oral Presentation Award)
4. **Foram U. Vaidya** and Chandramani Pathak presented poster on “Pluronic micelles encapsulated curcumin exhibits anti-proliferative response and manifests apoptotic cell death in multidrug resistant human breast adenocarcinoma cells” in XLII All India Cell Biology Conference and 2nd International Conference on Trends in Cell and Molecular Biology held on 21st – 23rd December, 2018 at BITS Pilani, K K Birla Goa Campus, Goa, India.
5. **Foram U. Vaidya**, Kishu Ranjan, Bhargav N. Waghela and Chandramani Pathak presented poster on “FADD regulates activation of NLRP-3 Inflammasome and promotes apoptotic cell death” in the International Congress of Cell Biology (ICCB), held on 27th -31st January 2018, organized by CSIR-Centre for Cellular & Molecular Biology (CCMB), Hyderabad, India.
6. **Foram U. Vaidya**, Rakesh Sharma and Chandramani Pathak presented poster on “Pluronic micelles encapsulated curcumin inhibits cell proliferation and manifests apoptosis in human breast adenocarcinoma cells” in Nanobioteck-2017, 2nd Annual Conference of Indian Society of Nanomedicine (ISNM) held on 6th – 8th December 2017, at Trivandrum, India.
7. **Foram U. Vaidya**, Rakesh Sharma and Chandramani Pathak , presented poster on “Anti-proliferative and apoptotic cell death response of aqueous soluble pluronic micelles encapsulated curcumin in cancer cells” in National Seminar on Recent Advances in Drug Discovery, held on 24th March, 2017 at Nirma University, India. (Best Poster Presentation award).

8. **Foram U. Vaidya**, Rakesh Sharma and Chandramani Pathak ,presented Oral Talk on “Structural characterization and evaluation of anti-proliferative and apoptotic potential of curcumin incorporated pluronic micelles in cancer cells.” in National symposium on Current research in cancer biology and therapy held on 7th-8th October, 2016 at University of Advanced Research , Gandhinagar, Gujarat.
9. **Foram U. Vaidya**, Rakesh Sharma and Chandramani Pathak presented poster on “Structural characterization and evaluation of anti-proliferative and apoptotic potential of Curcumin- incorporated Pluronic micelles in cancer cells” in 6th International Translational Cancer Research. Conference held on 4th-7th February, 2016 at Hyatt Regency, Ahmedabad, India.
10. **Foram U Vaidya** and Bhargav Waghela, presented Poster on “3D Bioprinting: The New era of Regenerative Medicine.” in poster competition held on 6th October 2015 at Indian Institute of Advanced Research, Gandhinagar, India. (Best Poster Award)
11. **Foram U. Vaidya**, Rakesh Sharma and Chandramani Pathak, presented poster on “Anticancer Activity Of Curcumin Encapsulated Pluronic Block Co-Polymer” at National Conference on “Herbal Drug Research: Opportunities and Challenges”, held on November 5-7, 2014 at B.V. Patel Pharmaceutical Education and Research Development (PERD) Centre, Ahmedabad.(Second prize).

- **PARTICIPATIONS IN CONFERENCES/ SYMPOSIA**

1. 8th International Conference of LASA, India on **“**Recent Advances in 3R’s and Laboratory Animal Science” held on 25th – 26th November, 2017 at Jawaharlal Nehru University, New Delhi, India.
2. 6th Annual Conference of Society for Mitochondrial Research and Medicine- India- International conference on Mitochondria in Health and Disease, held on 10th-11th February, 2017 at Jawaharlal Nehru University, New Delhi, India.
3. 3rd international Conference on Perspectives of Cell Signaling and Molecular Medicine held on 8th-10th January. 2017 at Bose Institute, Kolkata.
4. International symposium on Computational biology & DNA Computing jointly organized by GSBTM, DST and GoG held on 26th November, 2016 at DA-IICT, Gandhinagar, Gujarat, India.
5. International Conference on Human genetics & 39th Annual Meeting of the Indian Society of Human Genetics held on 22th -25th January 2014, Ahmedabad, India.

6. National Conference on Diabetes and its Complications: Search for Prevention and Cure – held on 6th -7th September, 2013 at institute of Life science, Nirma University, Ahmadabad, India.

Date: 13/07/2020

Place: IAR, Gandhinagar

Vaidya

(Foram U. Vaidya)

Signature of Ph.D. Student

Signature of Ph.D. Guide

Signature of Head of Department

13/07/2020

Signature of Dean (Research & Innovation